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Chief Scientific Officer

Sipuleucel-T for the Active Cellular Immunotherapy of Prostate Cancer

Hot Topic Symposium; iSBTc Annual Meeting – October 31, 2009
David L. Urdal

The following relationships exist related to this presentation:

- I am employed by Dendreon
- I own stock in Dendreon
- I will be discussing development of a Dendreon product candidate
Forward Looking Statements

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Sipuleucel-T for the Active Cellular Immunotherapy of Prostate Cancer

- Introduction to prostate cancer
- Development of sipuleucel-T
  - Clinical results
  - Regulatory milestones
  - IMPACT clinical trial results
- Conclusions
Natural History of Prostate Cancer

- **Castration**
- **Local Therapy**
- **Chemotherapy**
- **Death**

**Tumor volume & activity**

- **Asymptomatic**
  - Non-Metastatic
  - Androgen Dependent
- **Symptomatic**
  - Metastatic
  - Androgen Independent

**Time**
Androgen-Independent (Castration Resistant) Prostate Cancer Remains Unmet Medical Need

- Deadly disease
- Modest survival advantage seen with docetaxel-based regimens
- Majority of patients reject chemotherapy due to QOL impact
- Novel treatment approaches with acceptable safety profiles are needed
Sipuleucel-T is an autologous investigational active cellular immunotherapy product that activates the immune system against prostate cancer.
Sipuleucel-T: Patient-Specific Product

Day 1
Leukapheresis

Day 2-3
sipuleucel-T is manufactured

Day 3-4
Patient is infused

Apheresis Center

Dendreon

Doctor’s Office

COMPLETE COURSE OF THERAPY:
Weeks 0, 2, 4
Antigen Delivery Cassette™

- Composed of prostatic acid phosphatase (PAP) linked to granulocyte-macrophage colony stimulating factor (GM-CSF)
- Manufactured as recombinant protein antigen
- Robust, reproducible, well-characterized immune responses
Sipuleucel-T: Autologous APC Cultured with Antigen Delivery Cassette

Recombinant Prostatic Acid Phosphatase (PAP) fusion antigen combines with resting antigen presenting cell (APC)

APC takes up the antigen

Antigen is processed and presented on surface of the APC

Fully activated, the APC is now sipuleucel-T

Sipuleucel-T activates T-cells in the body

T-cells proliferate and attack cancer cells

The precise mechanism of sipuleucel-T in prostate cancer has not been established.
Pre-Clinical Rationale

- Antigen-loaded APCs isolated from peripheral blood showed clinical promise in lymphoma
- Prostatic acid phosphatase (PAP) highly expressed in prostate tissue
- Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) activates APCs
- Rat APCs, loaded with PAP+GM-CSF fusion protein, induced prostatitis

The Phase 3 Plan

- Two identical Phase 3 multi-center, double-blind, randomized, placebo controlled trials
  - D9901
  - D9902A
- Target population: asymptomatic, metastatic androgen independent prostate cancer
- Well-defined manufacturing process
- Potency and other release specifications established
Randomized, Double Blind, Placebo-Controlled Trials, Studies D9901 and D9902

Asymptomatic Metastatic Androgen Independent Prostate Cancer

- Sipuleucel-T Q 2 weeks x 3
- Placebo Q 2 weeks x 3

Primary endpoint: Time to Disease Progression
  - Radiographic, Clinical or Pain
  - Not PSA

Planned analysis: Overall Survival

2:1

Treated at Physician discretion

Treated at Physician discretion and/or Salvage Protocol

Survival
Sipuleucel-T Overall 3-Year Survival Intent-to-Treat Study D9901

p-value = 0.01 (log rank)
HR = 0.59
Median Survival Benefit = 4.5 months

Placebo (n=45)
Median Survival: 21.4 mos.

Sipuleucel-T (n=82)
Median Survival: 25.9 mos.

Survival Results Robust

- Treatment effect consistent across subpopulations
- Survival results confirmed by multiple sensitivity analyses
  - Adjustment for prognostic factors
  - Adjustment for Docetaxel
  - PCa specific mortality
  - Integrated analysis of D9901 and D9902A
Sipuleucel-T Laboratory/Clinical Correlations

Key product attributes:

- Total nucleated cell count
- CD54 count
- CD54 ‘upregulation’

The precise mechanism of sipuleucel-T in prostate cancer has not been established.
CD54 Upregulation Potency Assay for APCs

APCs cultured with recombinant antigen

Mean Fluorescence Intensity

Pre-culture

Post-culture
CD54 Upregulation by Treatment Week
Phase 3 Manufacturing Data

![Box plot showing CD54 upregulation ratio by treatment week. The x-axis represents weeks (Week 0, Week 2, Week 4). The y-axis represents the CD54 upregulation ratio ranging from 0 to 30.]
APC Activation Correlates with Survival (D9901 and D9902A)

- Sipuleucel-T (≥ median; n=73)
- Sipuleucel-T (< median; n=73)
Sipuleucel-T Potency Correlates with Survival

- Biologically relevant product measurement
- Independent of prognostic factors
- May support the efficacy findings
## Sipuleucel-T is Well Tolerated

### Table: Event Tolerability

<table>
<thead>
<tr>
<th>Event [n(%)]</th>
<th>Sipuleucel-T (n=82)</th>
<th>Placebo (n=45)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
<td>Grade 3-4</td>
<td>Grade 1-2</td>
</tr>
<tr>
<td>Rigors (chills)</td>
<td>45 (54.9)</td>
<td>4 (4.9)</td>
<td>4 (8.9)</td>
</tr>
<tr>
<td>Pyrexia (fever)</td>
<td>22 (26.8)</td>
<td>2 (2.4)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Tremor</td>
<td>8 (9.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Feeling Cold</td>
<td>7 (8.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Phase 3 Trial D9901
Regulatory Milestones

- The Center for Biologics Evaluation and Research (CBER)
  - Office of Cellular, Tissue and Gene Therapies (OCTGT)

- September 2005: Pre-BLA Meeting held with FDA:
  - Survival benefit observed in Study D9901
  - Supported by D9902A and the absence of significant toxicity
  - Will serve as the clinical basis of a BLA for sipuleucel-T

- November 2005: FDA granted Fast Track Status for sipuleucel-T
Regulatory Milestones (continued)

- August – November 2006: Submit rolling BLA
- January 2007: BLA accepted for Priority Review
- March 2007: FDA’s Cell, Tissue and Gene Therapies Advisory Committee
Cell, Tissue and Gene Therapy Advisory Committee

Key Questions to the Committee

- Is sipuleucel-T reasonably safe for the intended patient population?
  17 yes – 0 no

- Has substantial evidence of efficacy been established?
  13 yes – 4 no
The Preliminary Outcome

• Complete Response Letter – May 8, 2007
• Request for additional clinical and CMC information
IMPACT Phase 3 Study (D9902B)

**IMmunotherapy for Prostate AdenoCarcinoma Treatment**

- Randomized 2:1, double-blind, placebo-controlled
- ~500 men with minimally symptomatic, metastatic AIPC
- Enrolled at ~70 sites in North America
- Primary endpoint: Survival
- Secondary endpoint: Time to objective disease progression
- Special Protocol Assessment
- Positive interim or final survival analysis sufficient to amend BLA
Sipuleucel-T Immunotherapy for Advanced Prostate Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial

IMPACT STUDY

David Penson, MD, MPH
Professor of Urology
Vanderbilt University
For the IMPACT Study Investigators

American Urological Association Annual Meeting
April 28, 2009
Randomized Phase 3 IMPACT Trial
(IMmunotherapy Prostate AdenoCarcinoma Treatment)

Primary endpoint: Overall Survival
Secondary endpoint: Time to Objective Disease Progression
Statistical Analysis Plan

- **Stratification Factors**
  - Bisphosphonate use
  - Primary Gleason score
  - Number of bone metastases

- **HR and P-values**
  - Calculated from Cox model
    - Adjusted for PSA and LDH
  - 2 sided p-values
  - Log rank as sensitivity analysis

- **Analyses**
  - Interim: one
  - Final: p < 0.043 required for statistical significance
# Patient Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sipuleucel-T (N = 341)</th>
<th>Placebo (N = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median yrs (range)</td>
<td>72 (49 – 91)</td>
<td>70 (40 – 89)</td>
</tr>
<tr>
<td>Race, white (%)</td>
<td>89.4</td>
<td>91.2</td>
</tr>
<tr>
<td>ECOG status, 0 (%)</td>
<td>82.1</td>
<td>81.3</td>
</tr>
<tr>
<td>Gleason Score ≤ 7 (%)</td>
<td>75.4</td>
<td>75.4</td>
</tr>
<tr>
<td>Disease localization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone only (%)</td>
<td>50.7</td>
<td>43.3</td>
</tr>
<tr>
<td>Soft tissue only (%)</td>
<td>7.0</td>
<td>8.2</td>
</tr>
<tr>
<td>Bone &amp; soft tissue (%)</td>
<td>41.9</td>
<td>48.5</td>
</tr>
<tr>
<td>&gt;10 bone mets (%)</td>
<td>42.8</td>
<td>42.7</td>
</tr>
<tr>
<td>Bisphosphonate use</td>
<td>48.1</td>
<td>48.0</td>
</tr>
<tr>
<td>Prior docetaxel (%)</td>
<td>15.5</td>
<td>12.3</td>
</tr>
</tbody>
</table>
## Baseline Median Laboratory Values

<table>
<thead>
<tr>
<th>Test</th>
<th>Sipuleucel-T (N = 341)</th>
<th>Placebo (N = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum PSA, ng/mL</td>
<td>51.7</td>
<td>47.2</td>
</tr>
<tr>
<td>Serum PAP, U/L</td>
<td>2.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Alk. Phosphatase, U/L</td>
<td>99.0</td>
<td>109.0</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.9</td>
<td>12.7</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>194.0</td>
<td>193.0</td>
</tr>
<tr>
<td>WBC, 10^3/µL</td>
<td>6.2</td>
<td>6.0</td>
</tr>
</tbody>
</table>
IMPACT Overall Survival: Primary Endpoint
Intent-to-Treat Population

P = 0.032 (Cox model)
HR = 0.775 [95% CI: 0.614, 0.979]

Median Survival Benefit = 4.1 Mos.

Sipuleucel-T (n = 341)
Median Survival: 25.8 Mos.

Placebo (n = 171)
Median Survival: 21.7 Mos.
## Overall Survival Summary

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>75%</th>
<th>50%</th>
<th>25%</th>
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</thead>
<tbody>
<tr>
<td>Sipuleucel-T</td>
<td>341</td>
<td>15.1</td>
<td>25.8</td>
<td>41.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>171</td>
<td>11.0</td>
<td>21.7</td>
<td>35.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>% Survival (K-M estimates)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 Mos.</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>52.1</td>
</tr>
<tr>
<td>Placebo</td>
<td>41.2</td>
</tr>
</tbody>
</table>
Survival Consistency Between Population Subsets

Favors sipuleucel-T

- Bisphosphonate Use: Yes vs. No
- Primary Gleason Grade: ≥ 4 vs. ≤ 3
- No. Bone Metastases: > 10 vs. ≤ 10
- Disease Localization: Single vs. Bone + Soft Tissue
- ECOG Performance Status: 1 vs. 0
- Age: Above Median vs. Below Median
- PSA: Above Median vs. Below Median
- LDH: Above Median vs. Below Median
- Alkaline Phos: Above Median vs. Below Median
- Hemoglobin: Above Median vs. Below Median

Hazard Ratio (95% Confidence Interval)
Survival Results Confirmed by Multiple Sensitivity Analyses

- Primary Model (Adj. for PSA, LDH)
- Unadjusted/Log Rank
- Adjusted for Docetaxel Use
- PCa-Specific Survival

Favors sipuleucel-T

- Hazard Ratio (95% Confidence Interval)
  - 0.775, P = 0.032
  - 0.766, P = 0.023
  - 0.763, P = 0.036
  - 0.772, P = 0.036
Time to Objective Disease Progression

• Secondary endpoint
• Result
  – Independent radiologic review
  – HR=0.951 (95% CI: 0.77, 1.17); P=0.628 (log rank)
• Consistent with other trials in advanced prostate cancer
• Difficult endpoint to measure reliably and doesn’t correlate with overall survival
### Most Common Adverse Events (≥ 5%)

**Higher Rate in Sipuleucel-T (p ≤ 0.05)**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Sipuleucel-T N = 338</th>
<th>Placebo N = 168</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills</td>
<td>54.1</td>
<td>12.5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>29.3</td>
<td>13.7</td>
</tr>
<tr>
<td>Headache</td>
<td>16.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>9.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>5.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>
## Consistency Across Phase 3 Studies

<table>
<thead>
<tr>
<th></th>
<th>D9901* (N = 127)</th>
<th>D9902A* (N = 98)</th>
<th>IMPACT ** (N = 512)</th>
<th>Integrated** (N=737)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio</td>
<td>0.586</td>
<td>0.786</td>
<td>0.775</td>
<td>0.735</td>
</tr>
<tr>
<td>p-value</td>
<td>p = 0.010</td>
<td>p = 0.331</td>
<td>p = 0.032</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Median Survival Benefit (months)</td>
<td>4.5</td>
<td>3.3</td>
<td>4.1</td>
<td>3.9</td>
</tr>
<tr>
<td>36-Month survival (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sipuleucel-T</td>
<td>34%</td>
<td>32%</td>
<td>32%</td>
<td>33%</td>
</tr>
<tr>
<td>placebo</td>
<td>11%</td>
<td>21%</td>
<td>23%</td>
<td>20%</td>
</tr>
</tbody>
</table>

*Unadjusted Cox model & log rank

**Cox model adjusted for PSA and LDH
Summary

- Confirms improvement in overall survival for advanced prostate cancer
- Highly favorable benefit to risk profile
- Short duration of therapy
- Potential to create new treatment paradigm in oncology
- Amend BLA November 2009
Active Cellular Immunotherapy: A Potential New Treatment for Prostate Cancer

- **Androgen Dependent**
  - Local Therapy
  - Castration
  - Immunotherapies (sipuleucel-T)

- **Androgen Independent**
  - Non-Metastatic
  - Metastatic
  - Chemotherapy
  - Death

**Tumor volume & activity**

**Time**

**Asymptomatic**

**Symptomatic**
We are indebted to the patients who volunteered for this trial.

**IMPACT Study Investigators**

T. Ahmed    N. Barth    E. R. Berger    G. Bernstein    B. Bracken
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S. Hall    J. Hanson    C. Higano    R. Israeli
L. Klotz    R. Kratzke    R. Lance    J. Lech
D. McLeod    D. McNeel    B. Miles    M. Murdock
A. Pantuck    D. Penson    P. Perrotte    D. Pessis
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I. Shapira    D. Shepherd    N. Shore    E. Small
J. Vacirca    L. Villa    N. Vogelzang    M. Wertheim
J. Young

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Y. Xu

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D. George    V. Kassabian    J. Katz
P. Kantoff    R. Lemon    S.E. Martin
L. Garbo    T. Godfrey
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J. Lech
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R. Lance
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